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Evolution of drug-resistant tuberculosis: A tale of two species

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ABSTRACT **The history of the disease tuberculosis is briefly discussed. Now human societal failures have potentiated the evolution of drug-resistant strains of the tubercle bacillus in the United States and around the world. Until recently, this evolutionary change largely posed a threat to the health and survival of the individual in whom inadequate therapy promoted the drug resistance. However, the human immunodeficiency virus epidemic threatens to promote wholesale transmission of multidrug-resistant tuberculosis with the potential for immense morbidity and mortality. Reinforced treatment and control programs for tuberculosis are vital.**

Charles Darwin in his treatise *The Origin of Species* delineated the requirements for "evolution" as a process to explain the multitudinous forms of life on our planet. Broadly speaking, he posited that there must be diversity among the offspring of a species. Then there should be factors in the environment that create a selective advantage for the reproduction and survival of certain of those progeny. This preferential survival for that substrain might entail either a global or a localized survival advantage within a particular niche. In a general sense, but one of which I believe Darwin might approve, the emergence of drug-resistant tuberculosis represents such a phenomenon. Unfortunately, the environmental factor that is essential for the rising prevalence of drug-resistant tuberculosis around the globe is humankind. The interplay between the two species, *Mycobacterium tuberculosis* and *Homo sapiens*, and its role in the creation of strains of tuberculosis resistant to modern medications will be described below. And the emerging influence of yet a third species, the retroviriad human immunodeficiency virus (HIV), on this ecosystem will be considered as well.

The tubercle bacillus belongs to an unusual family of bacteria that are related to and presumably developed from the microbes that constitute the "living" component of soil. On the basis of studies of genetic relatedness as well as circumstantial evidence, the mycobacteria probably emerged from the soil to find a niche first infesting, then infecting various mammals and birds. *M. bovis* is the most common animal pathogen, afflicting a diverse array of mammals, including ruminants and primates. Webb in his 1932 historical overview of tuberculosis speculated that the tuberculosis germ was first systematically introduced into humankind when humans domesticated cattle around 5000 B.C. (1). Indeed, modern genetic analysis indicates an extremely high degree of DNA homology between *M. bovis* and *M. tuberculosis*, indicating that they are virtually the same species (2). Thus, it is reasonable to infer that the parent strain *M. bovis*—which does have limited invasive and disease-producing capacity within humans—has undergone subtle host adaptation within the human body to become the tubercle bacillus. In this process, the microbe has developed these unique traits: (*i*) its only significant natural reservoir is humans, (*ii*) it has substantially diminished virulence for most animal species other than humans, and (*iii*) it has developed a survival-transmission strategy that is unparalleled among the mycobacteria: airborne human-to-human spread.

Skeletal artifacts indicate that tuberculosis has afflicted humankind since at least 3000–5000 B.C. From the Hippocratic writings and the work of Galen we infer that tuberculosis, referred to then as "phthisis" (translation: "I am wasting") was highly prevalent in the Greco–Roman era. For the past 500 yr, tuberculosis has been pandemic in Europe and North America; at its apex in the 17th–18th centuries, the "White Plague" took the lives of 1 in 5 adults. In the 100 yr from 1850–1950, it is estimated that one billion persons died of tuberculosis.

Certainly one of the most meaningful achievements of modern medicine has been the development of curative therapy for this ancient scourge. Although it is a bacterium, the tuberculosis bacillus is highly resistant to the conventional antibiotics, such as penicillin or sulfa, which were developed in the 1930s and 1940s. Selman Waksman, a specialist in soil biology at Rutgers, while screening microbes recovered from the earth, came upon a substance elaborated by one of them with substantial activity against the tubercle bacillus in 1943–1944; this compound, streptomycin, was pressed rapidly into clinical use, with initial reports of its efficacy appearing in 1945 (3). Although useful in ameliorating disease manifestations, streptomycin alone was not sufficient to cure most cases. Microbiologists soon recognized that, while most bacilli in a population of *M. tuberculosis* were susceptible to the drug (they were killed rapidly by concentrations of the medication readily achievable in tissue), some mutant offspring were present that were resistant to the drug's effects. When streptomycin was given alone, it killed the vulnerable population but left behind the resistant mutants, a Darwinian selective process of "survival of the fittest." Without competition for the hosts' tissues, these bacilli then became the dominant subspecies.

Fortunately, two other medications were discovered shortly thereafter—*p*-aminosalicylic acid and isonicotinic acid hydrazide (isoniazid). Clinicians soon recognized that if all these drugs were given simultaneously, drug resistance did not emerge and lifetime cures of tuberculosis finally were achievable. Subsequent research showed that the explanation for this was as follows: (*i*) Random bacterial mutations that conferred resistance to individual drugs occurred infrequently during microbial replication, approximately once in 10^5–10^8 (4). (*ii*) These mutations were unlinked; therefore, the probability of a microbe spontaneously developing resistance to two drugs was the product of the individual risks or 1 in 10^5

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Abbreviations: HIV, human immunodeficiency virus; MDR-TB, multidrug-resistant tuberculosis.

$\times$ 1 in 10^6 = 1 in 10^{11} (3). Because the number of bacilli in a patient, even with extensive disease, rarely exceeds 10^9, it was highly improbable that multiresistant mutants would occur spontaneously (4). Thus, when isoniazid and streptomycin were given together, the isoniazid killed the mutants resistant to streptomycin and vice versa, ultimately eliminating the bacteria from the body.

In the 1950s and 1960s tuberculosis specialty hospitals (sanatoria) and clinics were widely available throughout the industrialized nations. Based on public fear of the disease and aggressive professional programs, successful treatment—despite the need for 24 months of drug therapy—was accomplished in the great majority of cases. However, as these two elements lost intensity and social disruptions became more pervasive in our society, adherence to treatment plans was eroded. Clinicians and public health authorities were hopeful that with newer, more powerful drugs the duration of treatment could be reduced sufficiently to combat noncompliance. But, despite reducing the required time from 24 to 6 months, irregular or incomplete adherence rose steadily over the past two decades (5).

As a consequence, the prevalence of drug-resistant strains of *M. tuberculosis* has risen dramatically in certain regions or populations. At the dawn of the treatment era, roughly 1–2% of strains of *M. tuberculosis* were seen to have significant drug resistance, almost universally to only one drug (6); in the 1960s and 1970s, that rate in the U.S. hovered around 3–5% (7, 8). However, over the past decade the national rate has risen steadily (9). In New York City, where a variety of elements, including poverty, substance abuse, and deteriorating public health programs, combined to confound tuberculosis control, 33% of tuberculosis strains recovered in April 1992 were resistant to at least one drug, and 19% were resistant to two or more agents (10). Tragically, in some developing nations where resources are limited, inadequate treatment programs have resulted in drug-resistant rates in excess of 30% (11).

How has this resistance evolved? In most instances it occurs because patients either cryptically discontinue one or more of their multiple drugs or take less than the prescribed dosage (12). Alternatively, physicians—who have become generally less familiar with tuberculosis as the incidence has diminished—prescribe inappropriately (13). In either scenario, insufficient numbers or dosages of drugs are administered, creating an environment that selects for survival of the drug-resistant mutants. Note that the drugs do not induce the mutations, only tip the balance in favor of the naturally derived variants.

In this manner, a gradually increasing portion of the world's tuberculosis cases involve drug-resistant organisms. Most drug-resistant cases have historically involved failed treatment in an individual (14); however, in some instances, these strains have been transmitted to a new patient, who then develops tuberculosis with pre-formed drug resistance (15). This has occurred with relatively low frequency, presumably because the metabolic compromises made by the microbes to enable drug resistance have made them modestly less virulent (16). And, in the normal host—whose immune system has a 90% chance of containing a tuberculosis infection for a lifetime—even a small reduction in pathogenic capacity would make transmission of drug-resistant disease quite uncommon.

Enter here a third species, the HIV. Unfortunately, the HIV epidemic is afflicting persons from countries and/or socioeconomic groups in which tuberculosis latent infection and disease are highly prevalent. Because HIV infects, disables, and kills the cell that is central to tuberculosis immunity—the $CD4^+$ or helper T lymphocyte—the viral epidemic has led to a dramatic upsurge in tuberculosis in regions such as sub-Saharan Africa and cities including New York, Miami, Los Angeles, Rio de Janeiro, Brazil, and Bangkok, Thailand, where HIV and tuberculosis are coincident. A particularly alarming aspect of these coepidemics is the rising level of multidrug-resistant strains of tuberculosis (MDR-TB) in certain communities. Large-scale, highly lethal epidemics of MDR-TB among HIV-infected/AIDS patients have been reported in at least eight hospitals in New York and Florida (17). Analysis of these nosocomial outbreaks demonstrates clearly that the impaired defenses associated with HIV disease facilitate the transmission of MDR-TB (18). And, as the proportion of tuberculosis associated with HIV rises in the United States and the world over the decades to come, we may anticipate that MDR-TB strains will comprise an expanded percentage of this morbidity.

The implications are profound: (*i*) Patients will die of tuberculosis due to inability to control the infection, (*ii*) the costs of treatment will soar, as more expensive drugs, extended therapy, and complicated surgery will be added to management, making cures unachievable for impoverished nations, and (*iii*) the highly effective prevention strategy of prophylactic treatment with isoniazid, a very inexpensive drug, to block the transition from latent infection to active disease will be rendered ineffectual.

In summary, human societal failures have potentiated the evolution of drug-resistant strains of the tubercle bacillus in the United States and around the world. Until recently, this has largely posed a threat to the health and survival of the individual in whom inadequate therapy has promoted the drug resistance. However, the HIV epidemic threatens to promote wholesale transmission of MDR-TB with the potential for immense morbidity and mortality. Reinforced treatment and control programs for TB are vital (19). Our response to this challenge will reflect on whether we deserve the appellation "sapient" or whether anthropologists will need to find another designation for our species.

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